

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Flack *et al.*

Appl. No.: 10/806,088

Filed: March 22, 2004

For: **Gossypol for the Treatment of
Cancer**

Confirmation No.: 1687

Art Unit: 1614

Examiner: Anderson, James D.

Atty. Docket: 225011

Declaration of Jon Theodore Holmlund, M.D. under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jon Theodore Holmlund, M.D., declare and state:

1. I am Chief Medical Officer and Vice President at Ascenta Therapeutics, Inc., the licensee of the above-captioned application. A copy of my curriculum vitae and list of publications is attached hereto as Exhibit A.

2. I have read and understand the above-captioned application and its prosecution history, including the office action dated August 4, 2006. I understand that the examiner has rejected the pending claims of the application as not enabling the practice of the claimed methods for their full scope. In my opinion, it is expected and predictable that (-)-gossypol may be used to treat a wide diversity of cancers.

3. Recent findings support the expectation that (-)-gossypol is useful for the treatment of a wide diversity of cancers in humans. It has been reported that modulating apoptosis (programmed cell death) suppressing members of the Bcl-2 family holds potential for treating cancer. See Shore, G.C., and Vaillet, J., *American Society of Hematology* 226-230 (2005) (Exhibit B). Shore and Viallet report that such apoptosis

suppressors (Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and A1) are often strongly elevated in diverse cancers, and have the potential to confer resistance to endogenous cell death stimuli and many cancer treatments. Moreover, multiple pro-survival members are typically up-regulated in a given cancer. Thus, new compounds are being tested which antagonize multiple Bcl-2 family proteins and induce apoptosis. GX15-070, a small organic molecule which reportedly binds to Bcl-w, Bcl-xL and Mcl-1 with a K_D value in the 0.5 μ M range, was found to exhibit antitumor activity as a single agent across diverse cancer cell types. (See pages 228-229 of Shore and Vaillet.) Thus, a small organic molecule which binds multiple Bcl-2 family members is expected to be useful for the treatment of diverse cancer cell types.

4. (-)-Gossypol binds to Bcl-2 and Bcl-xL with quite high affinities. (-)-Gossypol has K_i values of 320 nM and 480 nM to Bcl-2 and Bcl-xL proteins, respectively, in a competitive fluorescence polarization-based binding assay. A competitive binding assay showed that (-)-gossypol also binds to Mcl-1 protein, another anti-apoptotic Bcl-2 member, with a K_i of 180 nM. Thus, (-)-gossypol binds with high affinity to three apoptosis-suppressing members of the Bcl-2 family and, like GX15-070, is expected to be useful for the treatment of diverse cancer cell types.

5. (-)-Gossypol has been tested in the clinic for cancer treatment activity as a single agent in a clinical trial. As shown in Exhibit C, when (-)-gossypol (AT-101) was administered to patients with chronic lymphocytic leukemia (CLL),¹ activity was observed in terms of reduced cancer cell load in the peripheral blood (6 of 8 patients),

¹In this study, CLL patients received a total dose of 30 or 40 mg of (-)-gossypol either once daily or in divided doses either every day or for 21 of 28 days for a maximum of 12 weeks.

lymph nodes (8 of 8 patients) and spleen (6 of 6 patients with an enlarged spleen). In addition, one patient exhibited an improved platelet count and 2 patients exhibited improved disease symptoms. While these patients were not cured, they most certainly have been treated.

6. (-) Gossypol is also being tested in the clinic for activity against prostate cancer. In an ongoing study, as of 24 August 2006, two of twenty-three patients treated have experienced partial responses of the tumor marker prostate specific antigen (PSA), an indicator of clinical activity. Five others have experienced at least some improvement in PSA levels. Ten patients remain on treatment, including the two with partial PSA responses, while the others have discontinued treatment for progressive cancer or other reasons. For those patients who exhibited a partial response, their prostate cancer was certainly treated.”

7. In another study, 30 mg/day of (-)-gossypol was administered to a patient for the treatment of follicular lymphoma. As shown in Exhibit D, the patient experienced a 61% reduction in lesion size.² For this patient, the follicular lymphoma was certainly treated.

8. Additional evidence which supports the enablement of the present invention may be found in published U.S. Patent Application 20040214902, attached hereto as Exhibit E.

9. On page 5 of the Office Action, it is asserted that the claims are extremely broad insofar as they are directed to the treatment of different cancers with different

²In this study, the patient was treated with rituxamib for one year, then stopped. After about a month, the patient experienced progressive disease. The patient then

etiologies and treatment regimes. However, the breadth of the present claims is justified in view of what is known about strong elevation of the prosurvival Bcl-2 members in diverse cancer cell types, the fact that (-)-gossypol strongly binds to 3 members of this group, and the fact that (-)-gossypol has been found useful for the treatment of multiple types of cancer.

10. On pages 5-6 of the Office Action, it is asserted that no direction or guidance for the administration regimes necessary to treat all of the cancers with the various compounds are given. Further, it is asserted that the working examples are limited to the treatment of adrenal cancer with racemic gossypol and, thus, the Applicants have only provided specific direction or guidance for the treatment of adrenal cancer with racemic gossypol. I respectfully disagree with this assessment. Table 4 of the reissue application provides specific guidance as to dose ranges of (-)-gossypol (20-100 mg/day) that may be administered. These dose ranges encompass the doses of (-)-gossypol which have been found in practice (see above) to be useful for the treatment of various cancers with various etiologies by daily dosing as disclosed in the reissue application. Thus, the present application provides enough direction and guidance for one of ordinary skill in the art to practice the invention without undue experimentation.

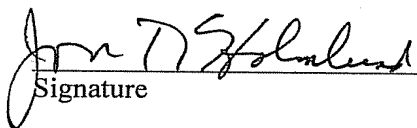
11. The Office Action also alleges that the practice of the invention is unpredictable, and that the therapeutic index for gossypol is extremely narrow. As the above clinical studies indicate, the therapeutic index for (-)-gossypol is wide enough to allow for the treatment of a number of different cancers with different etiologies.

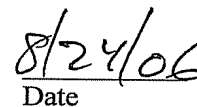
received (-) gossypol. SPD = the sum of the products of the greatest perpendicular diameter of the measured lesion (a measure of tumor volume). LN = lymph nodes.

12. In summary, all of the evidence to date provides the expectation that (-)-gossypol is useful for the treatment of diverse cancers. Accordingly, one of ordinary skill in the art would have every reason to expect that the method of treating cancers as claimed is enabled for its full scope.

13. I have read and understand 37 C.F.R § 10.18(b)

Respectfully submitted,


Signature


Date

CURRICULUM VITAE

NAME: Jon Theodore Holmlund, M.D.

EDUCATION: M.D., SUNY-Buffalo, 1984
B.A., Amherst College, 1979

MEDICAL LICENSURE: Maryland (D35450)—Inactive

SPECIALTY BOARD CERTIFICATION: Medical Oncology, 1991
Internal Medicine, 1987

BRIEF CHRONOLOGY OF EMPLOYMENT:

4/04-Date	Chief Medical Officer and Vice President, Development Ascenta Therapeutics, Inc. San Diego, CA
3/03-3/04	Vice President, Development Head of Clinical Development Isis Pharmaceuticals, Inc. Carlsbad, California
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8/97-12/97	Associate Medical Director, Drug Development Isis Pharmaceuticals, Inc. Carlsbad, California
1/96-8/97	Senior Investigator Biological Resources Branch, Developmental Therapeutics Program, and Investigational Drug Branch, Cancer Therapy Evaluation Program Division of Cancer Treatment, Diagnosis, and Centers National Cancer Institute National Institutes of Health Frederick, Maryland and Rockville, Maryland

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7/90-12/95	Project Officer, Program Director, and Senior Clinical Investigator Biological Resources Branch and Clinical Research Branch Biological Response Modifiers Program Division of Cancer Treatment National Cancer Institute National Institutes of Health Frederick, Maryland
7/88-6/90	Fellow in Hematology/Oncology George Washington University Medical Center Washington, D.C.
7/87-6/88	Instructor in Internal Medicine George Washington University Medical Center Washington, D.C.
7/84-6/87	Resident in Internal Medicine George Washington University Medical Center Washington, D.C.
7/81-6/82	Aide to Senator Pete V. Domenici (R-NM) United States Senate Washington, D.C.

PROFESSIONAL SOCIETIES: American Society of Clinical Oncology
American Association for Cancer Research
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HONORS/AWARDS: Sustained Superior Performance Award
Department of Cancer Treatment, Diagnosis, and Centers
National Cancer Institute
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Department of Cancer Treatment
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COMMITTEES/OTHER ACTIVITIES:

Fall 1995- Spring 1997	Core Courses in Biochemical Regulatory Engineering Program University of Maryland, Baltimore County:	
	Regulatory Issues in Biotechnology	Fall 1995
	Good Manufacturing Practices for Bio- Processes	Spring 1996
	Quality Control and Quality Assurance of Biotechnology Products	Fall 1996
	Biotechnology GMP Facility Design, Construction and Validation	Spring 1997
June 11-13, 1997	“The Mechanics of Preparing INDs and NDAs and FDA Regulations” Institute for Applied Pharmaceutical Sciences Center for Professional Advancement San Francisco, California	
1994-1997	Protocol Reviewer for <u>Physician’s Data Query</u>	
1991-1997	Reviewer for <u>Journal of the National Cancer Institute</u>	
1990-1997	Biologics Operating Committee, DCTDC/NCI/NIH	
1990-1997	Decision Network Committee, DCTDC/NCI/NIH (AD HOC)	
1991-1992	Organizing Committee for FDA/NCI Workshop on Preclinical Safety Testing of Monoclonal Antibodies (January, 1992, Bethesda, Maryland)	
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Abstracts

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